55. The purified polynucleotide of claim 11, wherein said polynucleotide comprises at least about 20 nucleotides.--

REMARKS

Introductory Comments

Claims 1-44 are pending. Claims 1-9, 17-24, 26-29, 31, 32, 34, 36, 37, and 40-44 are withdrawn from consideration. Claims 10-16, 25, 30, 33, 35, 38, and 39 are rejected. New claims 45-55 have been entered by this amendment.

The Examiner has rejected claims 10-16, 25, 33, 38 and 39 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner has rejected claims 10, 15, 16, 30 and 33 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The Examiner has rejected claims 10-16, 25, 33, 38 and 39 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement commensurate with the scope of the claims.

The Examiner has rejected claims 11-14 and 38-39 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner has rejected claims 10-16, 25, 30, 33, 35, 38 and 39 under 35 U.S.C. §102(b) asserting that the claims are clearly anticipated by U.S. Patent No. 5,574,007 to Zushi, et al.

The Examiner has rejected claims 10 and 35 under 35 U.S.C. §102(b) asserting that the claims are on sale and publicly used from Boehringer Mannheim Biochemical, 1991 catalog, page 557.

The Examiner has rejected claims 11, 14, 33, 38 and 39 under 35 U.S.C. §102(b) asserting that the claims are clearly anticipated by Hillier et al, EST database sequence accession AA456370.

The Examiner has rejected claims 10-16, 25, 30, 33, 35, 38 and 39 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Hillier et al, EST database sequence accession AA456370.

These rejections are believed to be overcome in part by the amendments and are otherwise traversed for reasons discussed below.

Overview of the Amendments

To the specification:

Basis for the amendment to the specification, adding reference to Sequence 819141, can be found in parent application 08/869,579, filed 5 June 1997, which was incorporated by reference in its entirety into the present application. The present application is a continuation-in-part of 08/869,579, filed 5 June 1997.

To the claims:

Claims 10, 11, 14, 15, 25, 30, 33, 38, and 39 have been amended without prejudice or disclaimer. Amendment of these claims is not intended to be an acquiescence in the Office's assessment of those claims in the 24 June 1999 Communication, and applicants expressly reserve the right to bring the subject matter of the original claims again in a subsequent, related application.

Basis for the addition of "sequence 819141" can be found in the parent application, incorporated by reference in its entirety in the present application, as discussed above.

Basis for the "purified" amendment to the claims can be found throughout the specification, for example, at the following location: page 15, lines 3-10.

Basis for the "90% identity" amendment to the claims can be found throughout the specification, for example, at the following locations: page 14, lines 26-35; and page 13, line 29, to page 14, line 7.

Basis for the "amino acid sequence of at least about 10 contiguous amino acids derived therefrom" amendment to the claims can be found throughout the specification, for example, at the following locations: page 12, line 31, to page 13, line 6; page 13, line 29, to page 14, line 7; and page 15, lines 32-35.

Basis for the "specifically binds" amendment to the claims can be found throughout the specification, and is discussed extensively in section 5, below.

Basis for new claims 44-46 can be found throughout the specification, for example, at the following locations: page 12, line 31, to page 13, line 6; page 13, line 29, to page 14, line 7; and page 15, lines 32-35.

Basis for new claims 47-54 can be found throughout the specification, for example, at the following location: page 12, line 31, to page 13, line 6.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

Addressing the Examiner's Objections and Rejections

1. Priority Claim

The Examiner asserts that "(T)he priority date awarded claims 10-16, 25, 30, 33, 35, 38 and 39 is the filing date of the present application 6/5/98 based on a lack of written description of full length sequences, for instance SEQ ID NO:5 and SEQ ID NO:17." Office action, dated 24 June 1999, page 2, paragraph numbered as "3".

Applicants direct the Examiner's attention to the accompanying appendix which presents an alignment of the sequences presented in the priority document (designated "priority sequence" in the appendix, including sequences 1554838 and 819141) with the

sequences presented in the present application. Applicants are entitled to their priority for at least nucleotides 1-329 of the consensus sequence and of almost the entire sequence of the polypeptide corresponding to the identified open reading frame.

For the polynucleotide sequences entitled to the priority claim the Examiner is directed, at least, to SEQ ID NO:3 and Figure 2 of priority application 08/869,579, filed 5 June 1997. Further, for polypeptide sequences the Examiner is directed, at least, to SEQ ID NO:6 (of priority application 08/869,579, filed 5 June 1997) which teaches approximately 108 amino acids of the 117 amino acid sequence taught in the present application.

2. Drawings

The Examiner has requested correction of the drawings to reflect appropriate SEQ ID NO identifiers. Applicants request that this requirement be held in abeyance until allowable subject matter is agreed upon between the applicants and the USPTO.

3. Rejection of Claims 10-16, 25, 33, 38 and 39 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 10-16, 25, 33, 38 and 39 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The basis of the Examiner's written description rejection is unclear to the applicants. The Examiner asserts that "the claims describing a BL127 polynucleotide, gene or protein, are directed to or encompass corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. None of these sequences meets the written description requirement provision of 35 U.S.C. §112, first paragraph." Office

action dated 24 June 1999, paragraph bridging pages 3-4. The Examiner concludes that "only SEQ ID NO's:1-5 and 17-20, but not the full breadth of the claims meet the written description requirement provision of 35 U.S.C. §112, first paragraph." Office action dated 24 June 1999, last paragraph page 4.

The wording of the Examiner's rejection sounds like a scope rejection yet it is couched in terms of a written description rejection. Clarification is requested.

Applicants submit that the claims clearly comply with the written description requirement. Each claim recites specific polynucleotide sequences, wherein the scope of each sequence is defined by a percent identity or specificity of binding limitation. Determination of percent identity is described in the specification at least on page 11, line 22, to page 12, line 5. Further, for claims reciting fragments of the claimed polynucleotides, the term "fragment" is defined throughout the specification and at least on page 13, lines 15-20. Applicants submit that the claims comply with the written description requirement of 35 U.S.C. §112, first paragraph, and withdrawal of the rejection is respectfully requested.

4. Rejection of Claims 10, 15, 16, 30, and 33 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 10, 15, 16, 30 and 33 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The Examiner has requested clarification in the claims regarding the recitation of "complements." The claims have been amended to provide this clarification. Accordingly, withdrawal of the rejection is respectfully requested.

5. Rejection of Claims 10-16, 25, 33, 38, and 39 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 10-16, 25, 33, 38 and 39 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement commensurate with the scope of the claims. In particular, the Examiner objects to the recitation of "% identity" in claims. The Examiner asserts that "(T)here are no parameters or algorithm given by which to decide if a given sequence shares 50% identity." Office action, dated 24 June 1999, page 6, lines 16-17.

The applicants respectfully disagree with the Examiner's position. On page 11, line 22, to page 12, line 5, the applicants discuss the use of available programs for calculating identity or similarity between sequences, in particular the applicants state the following:

> "Techniques for determining amino acid sequence "similarity" are well-known in the art. In general, "similarity" means the exact amino acid to amino acid comparison of two or more polypeptides at the appropriate place, where amino acids are identical or possess similar chemical and/or physical properties such as charge or hydrophobicity. A so-termed "percent similarity" then can be determined between the compared polypeptide sequences. Techniques for determining nucleic acid and amino acid sequence identity also are well known in the art and include determining the nucleotide sequence of the mRNA for that gene (usually via a cDNA intermediate) and determining the amino acid sequence encoded thereby, and comparing this to a second amino acid sequence. In general, "identity" refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Two or more polynucleotide sequences can be compared by determining their "percent identity." Two or more amino acid sequences likewise can be compared by determining their "percent identity." The programs available in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics

Computer Group, Madison, WI), for example, the GAP program, are capable of calculating both the identity between two polynucleotides and the identity and similarity between two polypeptide sequences, respectively. Other programs for calculating identity or similarity between sequences are known in the art."

The applicants submit that use of default parameters in the GAP program (as described in the User Manual) is routine and well within the abilities of one having ordinary skill in the art. This is essentially the same procedure the Examiner used to search the presently claimed sequences.

Absolute specificity and precision are not required in the claims. Claims need only reasonably apprize a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, Fed. Cir. 1986. The second paragraph of 35 U.S.C. §112 merely requires that an applicant set out and circumscribe a particular subject area with a reasonable degree of precision such that the metes and bounds of the invention are set forth. *Ex parte Head*, 214 USPQ 551, PTO Bd. App. 1981.

In addition, the applicants have introduced the language "specifically binds" to replace the language "selectively hybridizing." The specification provides extensive basis for use of this language. For example, on page 19, line 7-22 detection of an analyte is discussed wherein a specific binding member is prepared for binding to a target analyte such as a nucleotide target. On page 20, lines 1-13, a definition of "specific binding members is discussed, wherein a "specific binding member" is a member of a specific binding pair (see also, e.g., page 20, line 24, to page 21, line 3; page 21-35; and page 4, line 31, to page 6, line 4); that is, two different molecules where one of the molecules, through chemical or physical means, specifically binds to the second molecule. Specific binding pairs can include complementary nucleotide sequences. On pages 22-24, the specification describes how the sequences provided in the application may be used to produce polynucleotide sequences (for example, primers and probes; also see, e.g., page 13, lines 21-28; page 25, line 31, to page 26, line 4) which can be used in assays for the

detection of target nucleic acids in test samples, via specifically binding the polynucleotide sequences to the target. Probes may, for example, be designed from conserved nucleotide regions of the polynucleotides of interest or from non-conserved nucleotide regions of the polynucleotide of interest. The design of such probes for optimization in assays is within the skill of the routineer. Generally, nucleic acid probes are developed from non-conserved or unique regions when maximum specificity is desired, and nucleic acid probes are developed from conserved regions when assaying for nucleotide regions that are closely related to, for example, different members of a multi-gene family or in related species like mouse and man. Numerous examples are given in the specification that would allow one of ordinary skill in the art to determine the metes and bounds of the invention (e.g., Examples 1-9, pages 54-66). For example, selection of primers for use in polymerase chain reactions is described at least on page 26, line 5, to page 32, line 32, and exemplary conditions (including hybridization conditions) for such reactions are described in the Examples (e.g., Examples 3, 8 and 9).

Use of probes in fluorescent *in situ* hybridization (FISH) technology to perform chromosomal analysis is also described herein. Such an approach can be used to identify cancer-specific structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR-generated and/or allele specific oligonucleotides probes, allele specific amplification or by direct sequencing. Probes also can be labeled with radioisotopes, directly- or indirectly- detectable haptens, or fluorescent molecules, and utilized for *in situ* hybridization studies to evaluate the mRNA expression of the gene comprising the polynucleotide in tissue specimens or cells (page 25, lines 17-27; and Example 7, pages 62-63). Use of the polynucleotide sequences of the present invention in such technology is another example of specific binding of a polynucleotide sequence to a target.

The characteristics and properties of polynucleotides of the present invention for use in hybridization reactions (including probes and amplification primers) are extensively discussed in the specification in the context of specific binding (see, for

example, pages pages 26-32). Further, examples using polynucleotides in hybridization reactions are discussed in the application, including suitable reaction conditions (e.g., Examples 5, 6, and 7, pages 61-63).

The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI International v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 227 USPQ 577 (Fed. Cir. 1985). Further, the enablement requirement may be satisfied even though some experimentation is required. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986).

In view of the above arguments and amendments, the applicant submits that the claims are enabled and that the rejection of the claims under 35 U.S.C 112, first paragraph, should be withdrawn.

6. Rejection of Claims 11-14 and 38-39 under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 11-14 and 38-39 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner has asserted that claims 11-14 and 38-39 are vague and indefinite in the recitation of "BL172." The term "BL172" is described extensively throughout the specification (see, for example, pages 4-9; and Example 1). However, in order to facilitate prosecution applicants have removed this language from the claims.

The Examiner has objected to use of the word "gene" in the claims. Applicants believe the word "gene" has an art accepted meaning and that based on the teachings of the present specification analysis of the genomic organization of the claimed sequences is

within the ability of one having ordinary skill in the art. However, in order to facilitate prosecution the word "gene" has been deleted from the claims.

The court has consistently stated that claim language must be read in light of prior art and teachings of the specification. The standard is that the "definiteness of the language must be analyzed...in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). A claim which is clear to one ordinarily skilled in the art when read in light of the specification, does not fail for indefiniteness. *Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 932 F2d 1453, 1 USPQ2d 1536 (Fed. Cir 1986).

In view of the above amendments, the teachings of the specification and the level of ordinary skill in the present art, the applicants submit that the boundaries of the claims are capable of being understood by one of ordinary skill in the art. Therefore, the rejection of the claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

7. Rejection of Claim 10-16, 25, 30, 33, 35, 38 and 39 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 10-16, 25, 30, 33, 35, 38 and 39 under 35 U.S.C. §102(b) asserting that the claims are clearly anticipated by U.S. Patent No. 5,574,007 to Zushi, et al.

For prior art to anticipate under 35 U.S.C. 102 it has to meet every element of the claimed invention: such a determination is one of fact. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986).

The Examiner asserts that "(T)he use of fragment terminology refers to a single shared amino acid, encoded by three polynucleotides. Therefore Zushi et al anticipates all of the limitations of claims 10-16, 25, 30, 33, 35, 38, and 39." Office action, dated 24 June 1999, page 10, lines 4-6. First, the Examiner's assertion is incorrect. The specification defines fragments as having at least certain numbers of residues of

nucleotides or amino acids (see, for example, page 13, lines 15-20, and page 15, lines 32-35); in the context of the present invention fragment does not include a single shared amino acid. Second, in order to clarify the claims which contain the phrase "fragment" applicants have amended the claims to include minimum fragment lengths.

In view of the above amendments and arguments, the cited reference sequences cannot be said to teach all the elements of the present invention. Accordingly, there is no support for the claims being anticipated by the cited prior art under 35 U.S.C. §102(b) and withdrawal of the rejection is respectfully requested.

8. Rejection of Claim 10-16, 25, 30, 33, 35, 38 and 39 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 10 and 35 under 35 U.S.C. §102(b) asserting that the claimed subject matter was on sale and in public use as evidenced by the Boehringer Mannheim Biochemical catalog, 1991, page 557. The Examiner asserts that "(C)laim 10 is drawn to a test kit useful for detecting a BL172 polynucleotide fragment comprising a container containing at least one BL172 polynucleotide. Boehringer sells random hexamer primers capable of detecting sequence fragments of SEQ ID NO's:1-5 available in a container." Office action, dated 24 June 1999, page 10, paragraph numbered 17.

Applicants disagree with the Examiner's assessment. Clearly a random hexamer primer will not "detect" a BL172-specific polynucleotide -- it will randomly bind to a wide variety of "random" polynucleotides. However, in order to facilitate prosecution applicants have amended the claim to recite a "polynucleotide that specifically binds to a polynucleotide selected from the group consisting of SEQUENCE ID NO 1, sequence 819141, and complements thereof." The random primers cited by the Examiner will not specifically bind to the recited reference sequences.

Accordingly, there is no support for the claimed subject matter being on sale and publically used as asserted by the Examiner. Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

9. Rejection of Claims 11, 14, 33, 38 and 39 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 11, 14, 33, 38 and 39 under 35 U.S.C. §102(b) asserting that the claims are clearly anticipated by Hillier, et al., EST database sequence accession AA456370, dated 6 June 1997.

The Examiner has erroneously stated this rejection under 35 U.S.C. §102(b) when in fact the rejection should have been made under 35 U.S.C. §102(a). The filing date of the present application is 5 June 1998. The prior art being cited has a date of 6 June 1997. Accordingly, the prior art is only available under 35 U.S.C. §102(a).

The prior art sequences do not teach all the elements of the pending independent claims, as described in the following discussion. The accompanying figure (i.e., the Appendix) shows a rough alignment of the cited prior art sequence relative to the claimed sequences of the present invention. The alignments were based on the "query" sequence beginning and end locations as recited in the MPSRCH alignments. The following can be seen from the comparisons in the figures:

(i) both SEQ ID NO:1 and sequence 819141 have a priority date that precedes the cited art sequence AA456370 -- accordingly, both of these sequences are free of the art. Related claims include independent claims 10, 11, 33, and 39 (claim 39 is discussed further below);

(ii) it is unclear to the applicants how the claimed polypeptide sequences, in particular SEQ ID NO: 17, was searched. It seems, based on the MPSRCH results provided by the Examiner, that applicants' polypeptide sequence was used to search the database and a corresponding polynucleotide with the potential to encode the polypeptide was identified -- i.e., an alignment was found with the polynucleotide sequence AA456370. However it is not clear that the polypeptide sequence was previously known

in the art or whether it was only identified by hindsight reconstruction based on the sequence of the applicants' claimed polypeptide sequence. That is, was the polypeptide sequence corresponding to the polynucleotide sequence AA456370 published in the prior art, or was the polypeptide coding sequence identified based on a comparison to applicants' polypeptide sequence? If only the polynucleotide sequence was known in the prior art, then no guidance has been presented to show which frame of the polynucleotide sequence is the "correct" frame, that is the frame that matches applicants' polypeptide. Clarification is requested concerning how the polypeptide sequence corresponding to AA456370 was identified;

(iii) even if, for the sake of argument, the prior art taught the polypeptide sequence being relied upon by the Examiner, applicants taught 108 of the 117 amino acids of SEQ ID NO:17 in their priority document (see above "Priority" section). The polypeptide encoded by AA456370 corresponds approximately to the 92 carboxy-terminal residues of the 117 amino acids of SEQ ID NO:17 (i.e., the complete sequence of the polypeptide claimed as SEQ ID NO:17 is not taught by the prior art). Only approximately 9 amino acids of the carboxy terminus of the polypeptide were not explicitly recited in the priority document. In order to facilitate prosecution, independent claims including reference to SEQ ID NO:17 (i.e., claims 15, 25, 30, and 38) also include the following limitation: 90% identity to SEQUENCE ID NO 17, or an amino acid sequence of at least about 10 contiguous amino acids derived therefrom. Accordingly the cited prior art sequence cannot be said to teach all of the elements of the claimed invention; and

(iv) claim 39 further distinguishes over the prior art because the prior art does not disclose polynucleotide sequences comprising at least the claimed sequences or corresponding sequences having at least 90% identity to the recited sequences.

In view of the above amendments and arguments, the cited reference sequence cannot be said to teach all the elements of the present invention. The dependent claims distinguish over the prior art at least in view of their dependencies on the independent

claims. Accordingly, there is no support for the pending claims being anticipated by the cited prior art under 35 U.S.C. §102(a) and withdrawal of the rejection is respectfully requested.

10. Rejections of Claims 10-16, 25, 30, 33, 35, 38 and 39 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 10-16, 25, 30, 33, 35, 38 and 39 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Hillier, et al., EST database sequence accession AA456370, further in view of *Expression of Cloned Genes in E. coli*, Sambrook, et al., Cold Spring Harbor Laboratory, 1989.

The primary reference (Hillier, et al., EST database sequence accession AA456370) fails to meet the elements of the presently claimed invention for the reasons discussed above. The secondary reference cited by the Examiner does not make up for the shortcomings of the primary reference. The secondary reference only provides general teachings regarding manipulations of cloned sequences.

Accordingly, in view of the above information and arguments, applicants respectfully request that the rejection of the claims under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Please direct all further communications in this application to:

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Respectfully submitted,

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